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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/170,980	10/13/1998	JENNIFER L. HILLMAN	PF-0195-1DIV	7498

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	21

DATE MAILED: 07/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/170,980	Applicant(s) HILLMAN ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,18-20 and 25-32* is/are pending in the application.

4a) Of the above claim(s) *27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,18-20,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 27-32.

Since applicant has elected Group I, a prostate-associated kallikrein protein comprising the amino acid sequence of SEQ ID NO:1, or fragments thereof, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of new claims 27-32 directed to 1) a method for producing a polypeptide of SEQ ID NO:1, or a polypeptide comprising a naturally-occuring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1, 2) a method for screening an agonist or an antagonist of a polypeptide of SEQ ID NO:1, or a polypeptide comprising a naturally-occuring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1, 3) a method for screening a compound that specifically binds to a polypeptide of SEQ ID NO:1, or a polypeptide comprising a naturally-occuring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1, and 4) a method for screening a compound that modulates the activity of a polypeptide of SEQ ID NO:1, or a polypeptide comprising a naturally-occuring amino

acid sequence at least 90% identical to the sequence of SEQ ID NO:1, have been withdrawn from consideration as being directed to a non-elected invention and a prostate-associated kallikrein protein comprising the amino acid sequence of SEQ ID NO:1, or fragments thereof will be examined. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03. Newly submitted claims 27-32 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The elected invention and the inventions of new claims 27-32 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. 806.05 (h). In this instant case, a polypeptide could be used for several purposes, e.g. for biochemical assay, for making antibodies, and for making an affinity column to purify its antibodies. Further, the scope of the method claims 27-32 is different from the scope of the elected invention.

The requirement is still deem proper, and the finality is maintained.

Accordingly, claims 1, 18-20, 25-26, SEQ ID NO:1 are being examined.

It is noted that this application contains new claims 27-32 drawn to a nonelected invention. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

REJECTION UNDER 35 USC 101, UTILITY

Claims 1, 18-20, 25-26 remain rejected under 35 USC 101 for the reasons previously set forth in Paper No. 17.

Applicant argues that the claims have patentable utility and a well known utility based on 1) the strong chemical and structural homology of the claimed HPAK protein (SEQ ID NO:1) with a known human pancreatic kallikrein (54% sequence identity), and 2) the presence of three conserved, non-contiguous amino acid residues H65, D113 and S206, for serine protease, which is likely to confer chymotrypsinogen-like activity to HPAK, 10 conserved cysteines, which are structurally important and involved in the formation of 5 disulfide bonds, as well as one conserved amino acid D200, which is likely to confer chymotrypsinogen-like activity to HPAK, and at the amino terminal end, 24 amino acids which are similar to signal sequences important for kallikrein secretion. Applicant asserts that thus the claimed HPAK protein has numerous practical, beneficial uses in toxicology testing, drug development and the diagnosis of diseases characterized by expression of HPAK, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works.

Applicant recites the reference by Brenner et al, stating that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small.

Applicant submits a Declaration by Lars Michael Furness, describing how the claimed polypeptide can be used in protein expression analysis such as 2-D PAGE gels and Western blot.

Applicant's arguments set forth in paper No.17 have been considered but are not deemed to be persuasive for the following reasons:

The recitation of the reference by Brenner et al, and the submission of the Declaration by L.M. Furness is acknowledged. It is noted that however, the Declaration by L.M. Furness was not signed, and thus could not be considered.

Concerning Applicant's assertion that the claims have patentable utility and a well known utility based on the strong chemical and structural homology of the claimed HPAK protein (SEQ ID NO:1) with known human pancreatic kallikrein, and the presence of three conserved, non contiguous amino acid residues H65, D113 and S206, for serine protease, and 10 conserved cysteines, as well as one conserved amino acid D200, this argument is not persuasive because based on sequence identity alone, one could not predict the function of a protein, as taught by Bowie et al, Lazar et al and Burgess et al, all of record (See further discussion of this issue below).

I. The Applicable Legal Standard

Applicant summarizes case law on the utility requirement at pages 7-8 in the response.

II. Toxicology testing, drug discovery and disease diagnosis

A. Similarity with a human pancreatic kallikrein

Applicant asserts on pages 9-10 that because there is a substantial likelihood that the claimed SEQ ID NO:1 is functionally related to human pancreatic kallikrein, a polypeptide of undisputed utility, there is by implication a substantial likelihood that the

claimed polypeptide is similarly used. Appellant need not show any more to demonstrate utility.

This is not persuasive, because SEQ ID NO:1 has not been shown to be functionally related to a human pancreatic kallikrein. The only showing is that the protein of SEQ ID NO:1 presumbaly encoded by the claimed polynucleotide of SEQ ID NO:2 has 54% sequence identity to a human pancreatic kallikrein . Although the human pancreatic kallikrein has protease activy, neither the specification, nor the art of record teaches any association of SEQ ID NO:1 with a protease or chymotrypsinogen activity. Moreover, although SEQ ID NO: 1 has three non-contiguous conserved amino acids of serine proteases, and one conserved amino acid D200, there is no indication that these three non-contiguous conserved amino acids and said amino acid D200 would confer serine protease activity to SEQ ID NO:1. Similarly, although SEQ ID NO:1 has 10 conserved cysteines, which are involved in the formation of 5 disulfide bonds, there is no indication that these cysteines would form disulfide bonds in SEQ ID NO:1. Even if these cysteines form disulfide bonds in SEQ ID NO:1, and although formation of disulfide bonds would confer some structural conformation to SEQ ID NO:1, there is no indication that said conformation would confer serine protease activity to SEQ ID NO:1. Further, there is no teaching of consensus sequences that would suggest that the claimed SEQ ID NO:1 is part of the same human pancreatic kallikrein. The disclosed 24 amino acids at the amino terminal of SEQ ID NO:1 only possibly confers the secretion of SEQ ID NO:1, which is not a serine protease activity, and which is a property shared by numerous non-related secreted proteins. Moreover, with a 54%

sequence identity with a human pancreatic kallikrein, one could not predict that the claimed SEQ ID NO:1 has the same function as a human pancreatic kallikrein, based on the teaching of Bowie et al, Lazar et al, Burgess et al, and Bork (see further discussion below, under section III, The rejections are with merit.)

B. The use of SEQ ID NO:1 for toxicology testing, drug discovery and disease diagnosis.

Applicant argues at pages 10-12 in the response that the claimed polypeptide is useful as tools for toxicology testing, drug discovery, and the diagnosis of diseases that confer "specific benefits" to the public and that these uses are "well-established".

Specifically, Applicant refers to a Declaration by Lars Michael Furness, stating that the claimed invention is useful in two-dimensional gel electrophoresis analysis and Western blot used to monitor protein expression and assess drug toxicology (page 6, pages 10-12). Applicant further asserts on pages 12-13 that use of proteins expressed by human as a tool for toxicology testing, drug discovery and diagnosis of disease is a well-established utility as taught by Rockett et al and Nuwarysir et al, and that the claimed polynucleotide encoding the claimed polypeptide could be used in array experiments to study the effect of toxicological compounds, as indicated in the email from Dr. C. Afshari to the undersigned. Applicant concludes that there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening, and that the claimed polypeptide could be used in this manner.

It is noted that the Declaration by Lars Michael Furness was not signed, and thus is not considered.

It is also noted that toxicology testing and drug discover are not specifically recited in the specification as originally filed. Similarly, the use of two-dimensional gel electrophoresis analysis and Western blot to monitor the expression of SEQ ID NO:1, and assess drug toxicology is not specifically recited in the specification as originally filed.

It is further noted that SEQ ID NO:1 is a deduced amino acid sequence from a polynucleotide sequence of SEQ ID NO:2. The specification only discloses detection of mRNA of SEQ ID NO:2 in various cancer tissues. It is unpredictable that SEQ ID NO:2 would express and/or overexpress as proteins in cancer tissues, or in tissues involved in immune response, because it is well known in the art that a gene could be regulated at different levels, transcriptional, translational and postranslational regulation and that not all mRNA express as proteins (Alberts et al, Shantz et al, and Fu et al, all of record; see further discussion on translational control below).

Further, concerning the argument that that the claimed invention is useful in two-dimensional gel electrophoresis analysis and Western blot used to monitor protein expression and assess drug toxicology, the argument is not persuasive, because for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated by Applicant, all nucleic acids and expressed genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed SEQ ID NO: 1 are not disclosed in the instant specification. Neither

the toxic substances nor the susceptible organ systems are identified from drug screening using two-dimensional gel electrophoresis. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:1. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polypeptide in an array for toxicology screening or expression profiling is only useful in the sense that the information that is gained from the array or profile is dependent on the pattern derived from the array or profile, and says nothing with regard to each individual member of the array or profile. Again, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's polypeptide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the claimed polypeptide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding the polypeptide could be put.

Applicant states on page 13 that potential benefits to the public is enormous. Appellant cites 1) CV Therapeutics uses Incyte gene expression to identify the key gene associated with Tangiers disease, 2) reduction of time associated with target discovery

and validation by Incyte customers, and 3) over 50% of the drug targets in the pipline of Incyte customer are from Incyte database.

This is not persuasive because this assertion fails to address the utility of the individually claimed polypeptide. Further, in the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from a screening assay would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

The question at issue is whether or not the broad general assertion that the claimed polypeptides might be used for *any* diagnostic application, *any* drug discovery or *any* toxicology test (in the absence of a disclosure of *which* diagnostic application, *which* drug discovery or *which* toxicology test) would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has

definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

Applicant asserts, at page 14, that the use of the claimed invention as a tool for toxicology testing is a practical, real world use and is a "substantial" use. As used in toxicology testing, drug discovery and disease diagnosis the claimed invention has a beneficial use in research other than studying the claimed invention itself.

This is not persuasive because the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPO at 690. Here, there is no evidence that the claimed polypeptide has any utility.

Applicant asserts, at page 14, that there exists a market "for databases containing all expressed genes". This is not persuasive because this assertion fails to address the utility of the individually claimed polypeptide. The claims are to isolated chemical compositions, not to descriptive information included in a database.

III. The rejections are with merit

Concerning the issue of whether SEQ ID NO:1, which is a deduced amino acid sequence, exists in nature in tissues and/or overexpresses in tumors as compared to normal tissue, Applicant argues as follows: While steady state mRNA levels are not always directly proportional to the amount of protein in a cell, mRNA levels are routinely

used as an indicator of protein expression. Countless publications have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Applicant asserts that the examples recited by the Office represent unsual mechanisms of gene regulation. Moreover, Applicant asserts that mRNA levels are usually a good indicator of protein levels in a cell. Applicant recites a reference by Lewin et al, stating that for most genes control at the stage of initiation, i.e. by the interaction of RNA polymerase with its promoter is a major control point and probably the most common level of regulation.

Applicant further asserts that Applicant need only prove " a substantial likelihood" of utility, and that one would be imprudent in assuming that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner.

It is noted that Applicant has not recited any reference to substantiate Applicant's statement that mRNA levels are routinely used as an indicator of protein expression and that mRNA levels are usually a good indicator of protein levels in a cell.

Moreover, it is unpredictable that SEQ ID NO:1, which is a deduced amino sequence from the polynucleotide of SEQ ID NO:2, is expressed in cancer tissue in nature and /or overexpressed in cancer tissues as compared to normal tissues. The references by Alberts et al, Shantz et al, and Fu et al (all of record) clearly indicate that the presence of mRNA does not always dictate that such mRNAs are translated into proteins, and that the predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and

translation. For example, the p53 protein levels of expression do not correlate with levels of p53 mRNAs, and the p53 protein could be undetectable in cells expressing abundant amount of wild type p53 mRNA (Fu et al, of record, figure 3, and page 4396, second column). Further, the intracellular half-life of ornithine decarboxylase is less than 1 hour, and the post-translational regulation of the degradation of said enzyme is depending on the level of polyamines (Shantz et al, of record, page 110, first column).

Moreover, concerning Applicant's assertion that the examples recited by the Office represent unusual mechanisms of gene regulation, the arguments are not persuasive, because although some of the genes studied in the cited publication include special structural elements responsible for the observed translational regulation, the recited references by the Examiner are only some of examples of negative translational regulation. It is well known in the art that both translational and post-translational control is an important step in the control of gene expression, and although in some cases translational control could be specific and requires some structural pecularities, it is not necessarily that the translational control requires structural pecularities (Jansen M, 1995, Pediatric Res, 37(6): 681-686).

Thus, there is overwhelming evidence in the art that the level of a protein expression is not correlated with the level of its mRNA, and it is unpredictable that the claimed polypeptide of SEQ ID NO:1 is expressed in cancer tissue in nature and /or overexpressed in cancer tissues as compared to normal tissues.

At pages 16-19, Applicant argues that the precise biological role or function of an expressed polypeptide is not required to demonstrate uitility and that a utility may be

specified even if it applies to a broad class of inventions. Applicant argues, at pages 19-20, that the use of the claimed polypeptide as a research tool alone is a "substantial utility.

This is not persuasive because the proposition is not sufficient to establish utility for each member of the class. Specific utility must be shown or be evident for each member of the class. None of the utilities identified by Applicant, i.e. toxicology testing, drug discovery, disease diagnosis, treatment and prevention of diseases associated with SEQ ID NO:1 expression, have been demonstrated to be specific to SEQ ID NO:1. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of SEQ ID NO:1.

On the other hand, practical utility can be inferred if each and every member of the broad class possesses a common utility. However, SEQ ID NO:1 has not been shown to belong to a family of human kallikrein. The only showing is that the protein of SEQ ID NO:1 encoded by the claimed polynucleotide of SEQ ID NO:2 has 54% sequence identity to a human pancreatic kallikrein. Although the human kallikrein is a protease, neither the specification, nor the art of record teaches any association of SEQ ID NO:1 with protease activity. Moreover, although SEQ ID NO: 1 has three non-contiguous conserved amino acids of serine proteases, and one conserved amino acid D200, there is no indication that these three non-contiguous conserved amino acids and said amino acid D200 would confer serine protease activity. Similarly, although SEQ ID NO:1 has 10 conserved cysteines, which are involved in the formation of 5 disulfide

bonds, and although formation of disulfide bonds would confer some structural conformation to SEQ ID NO:1, there is no indication that said conformation would confer serine protease activity. Further, there is no teaching of consensus sequences that would suggest that the claimed SEQ ID NO:1 is part of the same human kallikrein family. The disclosed 24 amino acids at the amino terminal of SEQ ID NO:1 only possibly confers the secretion of SEQ ID NO:1, which is not a serine protease activity, and which is a property shared by numerous non-related secreted proteins.

There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. However, this is not the case for the claimed invention as no function in common with the human kallikrein family has been elucidated for the claimed SEQ ID NO:1.

Applicant argues on pages 21-23, that the Examiner failed to demonstrate that one of ordinary skill in the art would reasonably doubt the utility of the claimed invention, based on the homology or similarity of SEQ ID NO:1 to a human pancreatic kallikrein.

This argument is not persuasive because such evidence and scientific reasoning was presented in the grounds of rejection set forth under rejection under 35 U.S.C. 101, utility in previous Office actions.

Applicant asserts, at pages 21-23, that Bowie et al, Lazar et al, Burgess et al and Bork fail to support the outstanding rejections wherein the Examiner contended that the degree of amino acid identity between SEQ ID NO:1 and a human kallikrein are insufficient to establish that SEQ ID NO:1 shares the utilities of a human kallikrein. In particular, Applicant argues that the teachings of Bowie are irrelevant because they are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins and that these experiments are not relevant to Applicant's use of amino acid sequence homology to reasonably predict protein function. Further Applicant asserts that Bowie et al teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues, which have been conserved over the course of evolution. Applicant suggests that the amino acid differences between SEQ ID NO:1 and a human kallikrein are likely to occur at positions of minimal functional difference while residues that are conserved are likely those that are important for protein function because of natural selection. Further Applicant argues that Lazar et al and Burgess at al are not relevant because they are drawn to mutagenesis of particular amino acid residues with known importance to function and are not analogous to molecular evolution which is profoundly influenced by natural selection and are likely to represent substitutions that do not alter protein function.

This is argument is not persuasive because no particular function has been ascribed to any domain of SEQ ID NO:1, and it is unknown what function, if any, might be conserved for natural selection. Further, because the differences between SEQ ID

NO:1 and a human kallikrein involve 46% amino acid differences, as previously disclosed, the effects of these differences upon protein function cannot be predicted since as taught by Bowie et al, the amino acid sequence determines the shape and function of a protein and it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. The Lazar et al and Burgess et al references, although drawn to site directed mutagenesis studies, clearly demonstrate that even a single amino acid alteration can alter the function of a protein. It would be expected that with the disclosed differences in amino acid composition, at least some of the amino acids required for any common function would be altered. Although the proteins show some identity, such as three non-contiguous amino acids, and 10 cysteines, and one amino acid D200, no conserved region with any protease function has been identified. As previously disclosed, with these percent dissimilarities between the polypeptide encoded by the claimed invention and the prior art proteins, the effects of these dissimilarities upon protein structure and function cannot be predicted.

Applicant has submitted an additional reference by Brenner et al in order to support the assertion that the level of conservation observed between the claimed protein of SEQ ID NO:1 encoded by the claimed polynucleotide SEQ ID NO:2, and the prior art protein is indicative of a common function and hence, a common utility among the proteins. As stated by Applicant, Brenner et al has determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues and that local identity is particularly important since

40% or greater identity over at least 70 residues is reliable in signifying homology between proteins. Applicant demonstrates that SEQ ID NO:1 is a true homolog of a human kallikrein, based on the alignment criteria. Applicant states that one of ordinary skill would expect SEQ ID NO:1 to possess evolutionarily conserved structural and functional characteristics of a human kallikrein.

This is not persuasive. Although Applicant discloses 54% identity over 253 amino acids between a human kallikrein and SEQ ID NO:1, this is not persuasive because the relevance of the apparently arbitrarily chosen regions of identity is unclear since there is no suggestion, either in the specification or the art of record that any of these regions have been implicated in any particular serine protease activity, or is a consensus sequence of kallikrein. Further, although the claimed polypeptide has three conserved non-contiguous amino acids of serine protease, and 10 conserved cysteines, and one conserved amino acid D200, there is no indication that these amino acids or cysteines would confer serine protease activity. In addition, the 24 amino acids at the amino terminal of SEQ ID NO:1 only possibly confers the secretion of SEQ ID NO:1, which is not a serine protease activity, and which is a property shared by numerous non-related secreted proteins.Thus it would appear, if meaningful at all, that the similarities in these regions may be involved with as yet undefined biochemical properties and functions. Although it is possible that there is an evolutionary relationship between the claimed protein encoded by the claimed polynucleotide and the prior art proteins, based on the information in the art or record and in the specification, no particular serine protease function of SEQ ID NO:1 can be ascribed to the domains responsible for serine

protease function based on sequence identity to the prior art proteins. Although it is clear that methods are available to identify proteins with identity between primary amino acid sequences, it is well known and clearly understood in the art, as taught by Bowie et al that prediction of protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and it is also well known in the art, as exemplified by Lazar et al and Burgess et al that even a single amino acid change can alter protein function. The unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is further demonstrated by Bork, of record, who teaches the pitfalls associated with comparative sequence analysis for predicting protein function. Bork specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality.

Concerning Bork et al, Applicant asserts that Bork et al emphases "high-throughput technologies". Applicant asserts that human pancreatic kallikrein on the other hand was analyzed by both laboratory and computational sequence analysis, not the allegedly error-prone high-throughput technologies being denounced by Bork. Applicant asserts that the classification of human pancreatic kallikrein as a serine protease of the kallikrein family is credible scientific evidence, and has been substantiated by peer review.

This argument is not persuasive, because although the classification of human pancreatic kallikrein as a serine protease of the kallikrein family is credible by scientific evidence, and has been substantiated by peer review, the claimed classification of HPAK as a member of kallikrein has not been credibly validated by scientific evidence, and has not been substantiated by peer review. Further, Applicant has not shown that the computational prediction for the claimed invention is any more accurate than the prediction accuracy from several references well known in the art, recited in table 1, and reviewed by Bork et al (Bork et al, of record, table 1 on page 399).

In view of the information known in the art, it could not be predicted that a determination of a serine protease identity could be made based on sequence data alone. Further, given the differences between SEQ ID NO:1 and the prior art proteins, and given the unpredictability known in the art as evidenced by Bowie et al, Lazar et al and Burgess et al, as well as the unpredictability of the art of comparative sequence analysis to discern protein function from structure as taught by Bork, sequence identity alone cannot give a reasonable correlation between the structure and function of SEQ ID NO:1 and the disclosed prior art proteins.

IV. Particular or Unique Utility

Applicant argues, on pages 24-25, that practical real-world uses are not limited to uses that are unique or particular to an invention and that broad classes of inventions can satisfy the utility requirements so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class.

This is not persuasive because the requirement in any particular case is that practical utility can be inferred if each and every member of the broad class possesses a common utility. None of the utilities identified by Applicant, i.e. toxicology testing, drug discovery, disease diagnosis, treatment of cell proliferative disorders have been demonstrated to be specific to the polynucleotide encoding SEQ ID NO:1 or to the polypeptide encoded thereby. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polynucleotide encoding SEQ ID NO:1 or the polypeptide encoded thereby. Applicant's arguments have not been found persuasive and the rejection is maintained.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1, 20 and 25-26 pertaining to lack of a clear written description remains for reasons already of record in paper No. 17.

Applicant argues that the specification discloses SEQ ID NO:1 and naturally-occurring sequences of SEQ ID NO:1 that have at least 90% identity of SEQ ID NO:1. Given SEQ ID NO:1, one skilled in the art would recognize naturally-occurring sequences of SEQ ID NO:1 that have at least 90% identity of SEQ ID NO:1.

Applicant argues that the claimed genus is of narrow scope. Applicant asserts that In accordance with Brenner al, as little as 30% identity over at least 150 residues is a reliable threshold for establishing evolutionary homology between the two sequences. Applicant further asserts that the present claims recite a polypeptide comprising a

naturally occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, which has only 253 amino acid residues and that this variation is far less than 30% identity over at least 150 residues to SEQ ID NO:1. Applicant also asserts that the Examiner failed to provide any evidence that any class of proteins in which naturally occurring variants with 90% or greater sequence similarity do not function similarly.

Applicant's arguments set forth in paper No.19 have been considered but are not deemed to be persuasive for the following reasons:

Although Applicant describes the structure of SEQ ID No:1, Applicant does not define the claimed numerous variants in term of chemical structure, i.e. the chemical structure of the claimed variants are not disclosed in the specifcation. The claims 1, 20, 25-26 read on variants of SEQ ID No:1 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:1. The specification does not disclose which amino acid subjected to conservative or non-conservative substitution, or deletion, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed, because the function of SEQ ID NO:1 is not known (see the above Utility rejection). The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is

needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO:1 alone is insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants.

Therefore, applicant was not in possession of the claimed allelic variants.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 1, 18-20, 25-26 pertaining to lack of enablement due to lack of a well established utility remains for reasons already of record in paper No.17.

Applicant asserts that to the extent that the rejection under 112, first paragraph is based on the improper allegation of lack of patentable utility under 101, it fails for the same reason.

Rejection remains for the same reasons set forth under 101 rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 1, 20, 25-26, pertaining to lack of enablement for allelic variants of SEQ ID NO:1, remains for reasons already of record in paper No.13.

Applicant argues that given the information provided by SEQ ID NO:1, one of skill in the art would be able to routinely obtain a naturally-occurring amino acid sequences having at least 90% sequence identity to SEQ ID NO:1 by screening a cDNA library or

use appropriate PCR conditions for the relevant polynucleotides/polypeptides that already exist in nature. One of skill in the art need not make and test vast number of polypeptides that are based on the amino acid sequences of SEQ ID NO:1.

Applicant's arguments set forth in paper No. 19 have been considered but are not deemed to be persuasive for the following reasons:

The claims 1, 20, 25-26 read on allelic variants of SEQ ID No:1, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:1. The specification does not disclose which amino acid are subjected to conservative or non-conservative substitution, or deletion, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants that would exist in nature. No common structural attributes that identify the claimed variants are disclosed. No common functional attributes that identify the claimed variants are disclosed, because the function of SEQ ID NO:1 has not been convincingly demonstrated to be a serine protease, and because even a single amino acid substitution could dramatically affect the biological activity and characteristics of a protein, as taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record.Thus one of skill in the art would have expected a vast number of unrelated sequences, with unknown function, would be obtained by hybridization or PCR techniques based on the polynucleotide sequence presumably encoding the claimed amino acid sequence of SEQ ID NO:1.

REJECTION UNDER 35 USC 102

Claims 1, 25 remain rejected under 35 U.S.C. 102(b) as being anticipated by Fukushima, D et al, for the reason already of record in paper 17.

Applicant argues that with respect to "variants" encompassed by the claims, one must make a comparison along the entire length of SEQ ID NO:1.

Applicant's arguments set forth in paper No. 19 have been considered but are not deemed to be persuasive for the following reasons:

Applicant argues limitation not in the claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of thisplication or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

July 03/2002